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VOL. VI. NO. 1 NOVEMBER, 1912

TRANSACTIONS

OF THE

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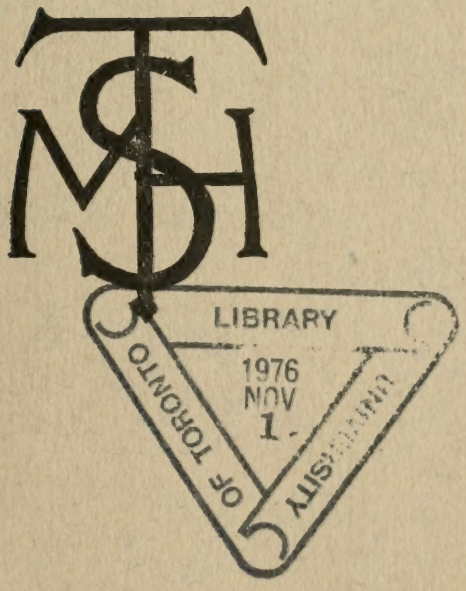
SOCIETY OF TROPICAL MEDICINE AND HYGIENE



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TRANSACTIONS OF THE SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

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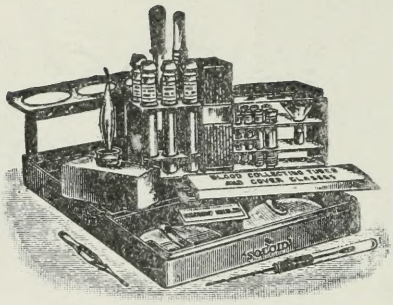

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Fig. 1.

"Chrome cell," lying on the left side of the uppermost polynuclear.

Fig. 2.

"Chrome cell," partially ruptured.

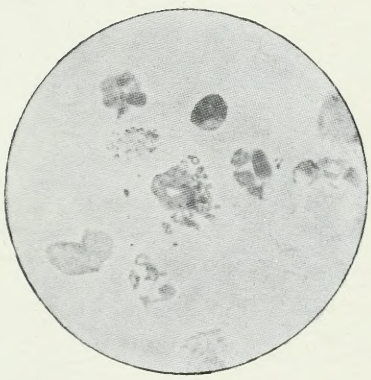

Fig. 3.

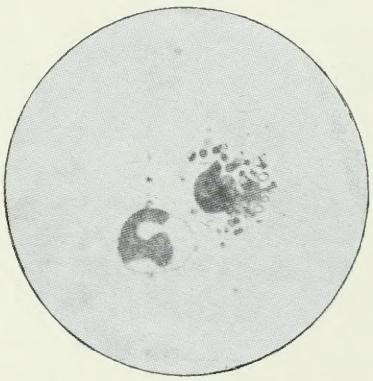

Fig. 4.

Cells from Case 3, shewing the large chromatin bodies and rings.

The specimens from which Figs. 1 and 2 were photographed had been stained by Leishman's method. Figs. 3 and 4 by Giemsa's method. Magnification, approximately 800 diameters.

Illustrations to accompany Sir William Leishman's paper.

TRANSACTIONS
OF THE
SOCIETY OF TROPICAL MEDICINE AND HYGIENE.

NOVEMBER, 1912.

VOLUME VI. No. 1.

Proceedings of a Meeting of the Society on Friday, October 18th, 1912.
SIR WILLIAM LEISHMAN, F.R.S., *President*, in the Chair.

The resignation of Dr. CARNEGIE BROWN of his position as Joint Secretary of the Society was announced, and a resolution expressing sincere regret at his resignation, and appreciation of the services he had rendered to the Society, which had been already passed by the Council, was unanimously endorsed by the Meeting. The President announced that Dr. G. C. Low had been appointed by the Council to take the place of Dr. CARNEGIE BROWN as one of the Honorary Secretaries of the Society.

THE ETIOLOGY OF BLACKWATER FEVER.

BY
SIR WILLIAM LEISHMANN, F.R.S.

I have felt strongly that one of the duties of your President, during the two years of his tenure of his office, should be to read a paper upon some branch of our subject, and it is mainly under this strong sense of duty that I am claiming your attention to-night by raising the subject of blackwater fever. I have selected this subject for two reasons, first because I think it a useful procedure from time to time to bring forward for discussion some disease of whose full understanding we are still ignorant, with a view to a free interchange of opinion on the debatable points, in a sense a sort of stocktaking which may impress on our minds what we are to consider as settled, and which are the points that await complete elucidation. Blackwater fever has not been mentioned among us for some time, and that is the first of my reasons for originating what I trust may be a full discussion of its etiology.

I feel, however, that I must offer a further excuse for introducing so thorny a subject to many whose personal acquaintance with the disease

so far exceeds my own. This second reason, or excuse, is that I have recently found certain curious bodies in the blood of cases of this disease which I wish to describe and demonstrate. These bodies naturally led me to search the literature upon the etiology of the disease, and this made me realise how very far we are from any general agreement on this point, the very foundation of the proper treatment and prevention of any affection. I am far from asserting that the bodies in question are etiologically connected with blackwater fever, such indeed would be a most unwarrantable suggestion at the present moment, but they have led me to formulate yet one more hypothesis as to its causation which I am anxious to submit to you for your consideration and criticism.

I propose in the first place to make a brief review of the various hypotheses and observations connected with the etiology of blackwater fever, with a view to arriving at an understanding of the points or factors which we may take as established, and upon which there is practically universal agreement. In the second part of my paper I shall describe to you the bodies I have encountered, and the hypothesis to which I have alluded, and I shall then endeavour to illustrate how far this hypothesis is consistent with the known facts.

I.

You are all familiar with the acute differences of opinion which, from time to time, have made themselves apparent in connection with the etiology of blackwater fever. One has not to read far before one encounters records and observations apparently altogether opposed to what, up to that moment, you had supposed to be an established fact. Going further, one finds what appears to be a reasonable explanation of these contradictions or a reconcilement of opposing views, only to find one's faith once again overturned by the reading of the next article. At the same time there is fairly general agreement upon certain points, and it is those which I am anxious to arrive at, for no hypothesis can be entertained seriously if it is inconsistent with the observed facts.

Lying at the outset of the question one point appears very clear to me, namely, that in many instances true blackwater fever has been confused with some other form of hæmoglobinuria, and herein is undoubtedly one of the causes of the contradictions and discrepancies to which I have alluded. One comes across records of cases in which the only symptom suggestive of the disease was the presence of hæmoglobin

in the urine. We are all familiar with the fact that this may occur in a number of other diseases, from the taking of various drugs, from fatigue, exposure, etc. Paroxysmal hæmoglobinuria has a very obscure pathology, and, should it occur in an endemic area of blackwater fever, or in an individual whom we might suspect to be liable to this, confusion and error of diagnosis must be very possible. At all events the recorded symptoms in many cases do not in all features correspond to the classical clinical picture. It is also very difficult to contrast with one another cases described at different times and from different localities, and the most valuable records are those of such as have had the opportunity of observing a considerable number of cases in the same locality, or preferably, in a hospital, and this over a considerable time. Odd cases here and there, observed often under the most trying conditions for accurate enquiry, are apt, I imagine, to lead to hasty and unjustified generalisations. In attempting to review the literature of the published cases, this uncertainty crops up frequently, and it is, I feel sure, one of the causes of the divergence of opinion on the etiology of this disease.

I could not hope to give you anything approaching a complete analysis of the records; I neither feel myself qualified to do so, by reason of my very limited personal acquaintance with the disease, nor would the limitations of a paper suffice for such an end. I shall therefore proceed to give, in mere outline, what I take it are the alternative views current at this time, and the main factors telling, respectively, for and against these.

It is convenient to follow the classification commonly adopted, in which all hypotheses are grouped under one of the following four heads:—

1. That it is a manifestation of active malaria.
2. That it is quinine poisoning.
3. That it is due to a specific organism.
4. That it is a result of a condition brought about by previous malarial infection.

1. The first of these, that blackwater fever is simply a form of malaria, is little advocated to-day. It is abundantly clear, that, whatever influence previous malaria may have, it alone cannot be held responsible for the syndrome of symptoms constituting hæmoglobinuric fever. It is undoubted that cases have occurred in which no evidence of malaria

could be detected either before, during, or after the paroxysm, and, although parasites may be found in a very large majority of the cases, particularly on the day before the attack, there is no direct relationship between their numbers and the severity of the subsequent attack of blackwater fever. The theory that blackwater fever may be due to the malignant tertian parasite alone has been disproved, since it has been found, though rarely, associated with both quartan and benign tertian, and there is little in support of the conjecture that it may be the result of a sudden increase in the virulence of the parasite. At the same time, many are agreed that an attack of malaria may act occasionally as an exciting cause of the disease. One of the strongest points against the disease being actually a manifestation of, and due to the malarial parasite, is the fact that an attack is altogether uninfluenced by quinine.

2. Quinine poisoning, as the essential cause of blackwater fever, is still a matter of debate. This question is especially complicated by the well known fact that the administration of this drug, in the case of individuals who have at some time suffered from malaria, may be followed by an attack of hæmoglobinuria. The recorded cases of this nature are too numerous and too well attested to admit of any doubt that this is the case, but I fancy there are few now who would go so far as to say that quinine poisoning was the sole cause of the disease. The problem is a very involved one; on the one hand we have records of cases such as that of Sir PATRICK MANSON[1] where an attack of hæmoglobinuria could be produced at will by the ingestion of even a small dose of quinine, and the records of cases such as KETCHEN'S[2] where a series of seven consecutive attacks in the same individual were each the sequel of a dose of quinine. On the other hand, against its being due to quinine alone we have such strong points as the following, all well established: (i) No cases have been recorded in non-malarious countries in which quinine, given for some other disease, has caused blackwater fever. (ii.) Numerous well-authenticated cases are on record in which blackwater fever developed in individuals who had either never had quinine at all, or who had had none for a considerable time before the attack. (iii.) A man may have an attack of blackwater fever subsequent to a dose of quinine, and yet may afterwards take even large doses of the drug with impunity. (iv.) There appears to be no relation between the size of the dose, the channel of administration or

the particular salt employed, and the attack, although each of these has at times been suggested as the essential factor.

I cannot attempt a fuller analysis of this much debated question in which there are still many who follow KOCH'S views on the subject, notably some of the Greek school, and will only conclude that we must admit that quinine, though almost indubitably not the sole cause of the disease, may be, and frequently is, one of the exciting causes of an attack. There are many points into which one would like to enter if time permitted, such as the question of personal idiosyncrasy to quinine, the bearing of the cessation or great diminution of the excretion of quinine in the urine during the attack on the causation of the hæmoglobinuria, but one must pass on.

As to the mechanism by which the drug is supposed to cause the hæmoglobinuria, most hold that it acts directly on the malarial parasites, and that these when destroyed liberate a toxin with hæmolytic powers for the red cells. I gather that few even of the strongest supporters of the quinine hypothesis do not admit, however, that some other factor is required to explain all the facts.

3. As to the third view, namely, that the disease is caused by a specific virus, a possibility that few even of the strongest advocates of the alternative hypotheses deny, there is at present no proof. There has been a general feeling that if such a specific organism were found it would satisfactorily clear up many of the points which remain mysterious in connection with the disease, but, in view of the persistent failure to establish the claims of such parasites as have been described, this hypothesis has been almost abandoned. On the analogy of diseases of animals due to piroplasmata, so often associated with hæmoglobinuria, a similar organism has been suggested by SAMBON and others in blackwater fever, but the most careful search has failed to reveal, or at least to confirm, anything of this nature. In fact, in view of the enormous amount of painstaking blood investigation by the most skilled hands and eyes, we may I think take it as proven that no special intra-corpuscular parasite of the red cells exists in this disease. The suggestion that a new species or an exceptionally virulent species of malaria may be the cause has not been established, and there are many facts telling against such a supposition. Whether the fuchsin-staining spirochæte of ANTHONY, whose cultures reproduced the disease on inoculation into animals, has been seen by anyone else I am unable to discover.

One of the arguments most frequently urged against there being a specific virus, apart from the fact that none has yet been seen, is the fact that the disease only rarely attacks new comers to an endemic area. This argument, however, appears to me of doubtful cogency; so many other things come into play besides the mere duration of residence, and, moreover, although it is admitted that the general statement is correct, there are on record a number of instances in which new comers have been attacked, one even within ten days of his first arrival in the endemic zone, while there are quite a number which occurred within six months of arrival.

Altogether, it may be said that although there is little beyond conjecture in support of the disease being one, *sui generis*, there are many indications that a properly accredited virus would not be unwelcome to many of those who have wide knowledge of the disease, and who are not altogether satisfied with any of the current explanations.

4. I have left to the last the view which is, I think, most widely current, namely that blackwater fever, although not actually a manifestation of malaria, is a condition brought about by previous malarial infection. If there is one point upon which everyone is agreed in this most puzzling of diseases, it is that there is a close and constant association with malaria. Although cases are on record in which it is stated that there was no evidence of antecedent malaria yet such cases have always occurred in endemic malarious countries, and none, so far as I am aware, have been reported in individuals who had never resided in such a country or district. It is necessary to keep clearly in one's mind the distinction between this proven or possible malarious infection prior to the attack of hæmoglobinuric fever, and the actual demonstration of parasites in the blood at the time of, or immediately preceding the paroxysm. As already mentioned, the latter is certainly not an absolutely essential preliminary, but the former, with equal or greater certainty, may be said to be indispensable. This appears to me so clear that I do not think any hypothesis of etiology which fails to take this fact into account can hold for a minute.

I have no time to discuss in detail the apparent discrepancies between the geographical distributions of blackwater fever and malaria, on which there has been so much said and written; it appears certain that earlier objections to any close relationship between the two can no longer be

upheld since recent researches have, in so many instances, shewn that blackwater fever is present, though perhaps rare, in countries hitherto believed to be free from it. Admitting this freely, however, there still remain in the minds of most of us instances of districts or countries, personally known to us, in which, though malaria is present in intense and widespread form, yet cases of blackwater fever have not yet been observed. It does not suffice, I think, as has been done, to comment on such cases that it must have been present but has been unrecognised by the local physicians; criticisms of that sort are easy to make, but are, I think, neither generous nor justifiable. Few I think will question the statement that discrepancies still remain unaccounted for in the geographical distributions of malaria and blackwater fever.

No better exposition of the hypothesis of the necessity of antecedent malaria can exist than is to be found in the admirable work of DEEKS and JAMES[3] in which they record the results of their observation of 230 cases of hæmoglobinuric fever in the Canal Zone of Panama. This is no doubt familiar to most of you, and I shall only recapitulate the conclusions which they reached as the result of their painstaking observations. In their essentials, these conclusions appear to me to represent fairly accurately the etiological views on blackwater fever most widely held at the present moment; they were as follows:—

1. Hæmoglobinuric fever is a manifestation of malarial toxicity, for the most part brought about by repeated attacks of malaria.

2. It may appear coincidently with an acute malarial paroxysm.

3. It may be determined by any depressing influence.

4. It may be induced by the administration of quinine.

5. Quinine alone, or malarial infection alone, do not cause hæmoglobinuria, but one or both of these conditions, plus the toxin eventuated during the course of one or more malarial attacks.

In another part of their work they add that, in their opinion, blackwater fever invariably manifests itself when certain conditions relative to the epidemiology of malaria, and to that of no other disease, are present. These conditions are:—

1. The presence of a population non-immune to malaria.

2. The prevalence of malaria in such quantity as to produce an almost continuous infection of this population.

3. A large proportion of æstivo-autumnal malaria; because the amount of blackwater fever is in direct proportion to the intensity of this variety.

4. The neglect of prompt and continuous administration of quinine, especially in primary attacks, to persons non-immune against malaria.

They assert that in every locality, without exception, where these conditions obtain, hæmoglobinuric fever is found. I should be glad to hear from those present how far they are in agreement with this assertion in the light of their personal knowledge of the disease.

It appears then that we may take it as certain that previous malaria, or, if I may put it in another form, exposure to the conditions which induce malaria, is a necessary antecedent to true blackwater fever. It is, however, as generally granted that, in addition to this predisposing cause, there is further required a determining or exciting cause. No lack of these exciting causes have been reported and suggested, and, in almost all, the evidence is so clear that we are bound to accept them as having an important, albeit secondary rôle in the etiology of the disease. As has already been said, an actual attack of malaria itself may be such an exciting cause, while quinine is so commonly recorded as such that it has, as we have seen, been promoted by some to the rank of a primary cause; be that as it may, there is at least no doubt of the fact that, in certain individuals it acts as the exciting or determining cause. Exposure to cold, damp, fatigue or over-exertion, change of residence, for instance from the interior of an endemic country to the coast, or return from the tropical to the home country, have often been reported as the apparent exciting cause of an attack, which, at all events, has not infrequently coincided with such movements.

Of the rarer secondary or exciting causes which have been mentioned I may, without attempting to give an exhaustive list, enumerate the following:—alcoholism, syphilis, gonorrhœa, association with the rheumatic diathesis, diminished alkalinity of the blood, kala azar, a meat diet, mental states and emotions, the existence of a kidney lesion, the ingestion of special articles of diet, such as beans, figs, snails, and absinthe. and even the smell of certain substances. I have said nothing of the very long list of drugs which are known to be capable at times of causing hæmoglobinuria, apart altogether from antecedent malaria or residence in an intensely malarious country, but you will realise that it is

inevitable that a certain number of cases of hæmoglobinuria occurring in the tropics must have been caused by drugs and it can hardly be doubted that some have been diagnosed as blackwater fever.

The above list affords abundant opportunity for a critical consideration of the evidence connecting each with the disease we are discussing, but, apart from considerations of time, such an analysis would not appear to serve any very useful purpose. Again we may generalise in the statement that the paroxysm of hæmoglobinuric fever is usually called forth by the action of some secondary or exciting cause, and that the most common of such causes appear to be exposure to cold and the exhibition of quinine.

Within recent years a large amount of experiment and research has been directed to the elucidation of the actual mechanism of the hæmolysis which takes place on so colossal a scale and with such great suddenness. In view of the close connection with antecedent malaria much of this work has been directed towards the elaboration of some theory which would satisfactorily explain the appearance in the blood of a specific malarial hæmolysin. It cannot be said that any of the theories put forward are very convincing; the larger part of them assume that the antigen which calls forth these specific antibodies is a toxin liberated from the malarial parasites when these are suddenly destroyed, for instance by the action of a dose of quinine. Others assume that as the specific hæmolysin is formed, by repeated attacks of malaria, an anti-hæmolysin also makes its appearance, and that these exist in the blood side by side until some agency, such as one of the exciting causes mentioned above, comes into action and disturbs the equilibrium between them, thus permitting the hæmolysin to act suddenly upon a large number of cells. The correct interpretation of the hæmolytic phenomena appears to me to bristle with difficulties, and, ingenious as are many of the theories—notably that of CHRISTOPHERS and BENTLEY[4] who bring evidence to shew that the hæmolysin is probably derived as a result of auto-immunisation against the individual's own red cells, which are constantly being phagocyted in the spleen and elsewhere—it cannot be said that any of them find universal acceptance. BARRETT and YORKE[5] have shewn that quinine cannot be held responsible *per se*, since it would have to be present in the blood in toxic dose before it could produce hæmolysis; they believe that the hæmoglobinuria is the result of an antecedent hæmoglobinæmia and that the anuria is due to mechanical blocking of the urinary tubules.

It appears to me of doubtful value to attempt to apply to these little understood processes of protozoal immunity the doctrines of bacterial immunity in terms of EHRLICH'S hypothesis; it is, I think, still far from clear that protozoal immunity, when it exists, follows the same lines as bacterial immunity, at all events there is little satisfactory evidence in such diseases of the appearance of such substances as lysins, agglutinins, precipitins, opsonins, etc. A recent theory of CLELAND'S[6] that in the phenomenon of hæmolysis we have an expression of an anaphylactic condition, brought about by the presence in the serum of a foreign protein in the shape of disintegrated merozoites, though ingenious, will hardly bear close inspection.

Before going on to the second portion of my paper I shall conclude this very curt and inadequate review of our present knowledge of the etiology of blackwater fever by summarising a few of the principal conclusions to which my study of the subject has led me, and which appear to be accepted fairly generally. I trust that they may call forth from among you expressions of dissent or agreement, which will serve to shew how far we are unanimous on these points, and, if we differ, which are the points that we are to regard as still matters of opinion awaiting final settlement. In this way, I believe, our discussions can afford substantial assistance to the progress of tropical research.

My interpretation, then, of the published observations and hypotheses in connection with the etiology of blackwater fever leads me to regard as fairly well established the following points:—

1. It is only encountered in those who have either suffered from malaria or who have lived for some time in a country in which they must constantly have been exposed to the danger of malarial infection.

2. One attack of blackwater fever confers no immunity against further attacks, but negro and other native races inhabiting endemic zones exhibit a certain degree of immunity. Whites and alien natives introduced into an endemic zone are most liable to the disease, but, as a rule, only after a certain period of residence.

3. Immunity to malaria appears to go hand in hand with immunity to blackwater fever, and measures which protect against malarial infection are also prophylactic against blackwater fever.

4. The regions of most intense malarial infection are those which in

blackwater fever occurs, but there exist also extremely malarious regions in which it is either extremely rare or absent.

5. In the majority of cases an exciting cause is needed to produce the hæmoglobinuric fever; the most frequent appear to be quinine and exposure to cold.

6. The precise mechanism of the sudden and extensive hæmolysis is not yet fully understood; there is certainly no direct relationship to the number or severity of the antecedent attacks of malaria, or to the number of malarial parasites present at the time of the attack.

II.

Turning now to the second part of my paper, I shall proceed to describe the cell-inclusions which I have encountered in the blood from cases of blackwater fever. I feel that I need not spend much time over this description since I have already given an account of them in two notes in the *Journal of the Royal Army Medical Corps*,[7 and 8] accompanied by illustrations, to which I would refer any who may feel sufficiently interested. In these notes I dealt with the results of my examination of films of blood from three cases; since then I have had the opportunity of examining films from nine other cases, making a total of twelve. I am deeply in the debt of those to whom I owe these specimens, and I wish particularly to acknowledge the very valuable assistance which I have received from Mr. H. J. Read, C.M.G., of the Colonial Office, for circulating to colonial medical officers a note of my requirements.

The cases from which these blood films were taken occurred in the following places:—Uganda (Kampala and Entebbe), Sierra Leone, Gold Coast (Quittah), South Africa (Rand), Lagos, and Southern Nigeria.

In two instances, films taken on successive days after the onset of the disease were available for study, but in no case was there a sample of the blood before the onset of hæmoglobinuria. The majority of the films were accompanied by a note of the clinical symptoms, treatment, etc., but in some this was not available. In the majority, the clinical account gave a clear and characteristic picture of a typical attack. The only other point I need mention is that in those instances in which malarial parasites had been searched for none had been found. In connection with this last point, I may add that in all but two of these cases I can confirm this absence of parasites: in one I found a pigmented leucocyte,

and in the other a few rings, after several hours' search, a time which naturally the busy colonial surgeon can rarely afford.

The general aspect of these films shewed no great uniformity. In most there was a leucocytosis, usually polynuclear in character, and there were almost always present, sometimes in very large numbers, a peculiar type of very large mononuclear cell with coarsely reticular protoplasm, which I believe to have been of endothelial origin. Other curious cells, which may or may not have some significance, I shall allude to in a moment.

The small number of cases and the want of uniformity in the time of taking the films render futile any attempts to draw conclusions as to the usual blood picture during the attack. This, however, is of little moment, since so many valuable records already exist in connection with this subject. I would only instance the frequency with which I have encountered neutrophil myelocytes, normoblasts and megaloblasts and TÜRK's cells as pointing to the involvement of the marrow, but whether this points to a primary affection of this tissue, or is only an indication of the rapidity with which compensatory mechanism comes into action, I am unable to say.

As to the inclusions, these I have encountered principally in the large mononuclear cells which I take to be endothelial in origin, and to have been disrupted from the walls of the smaller blood-vessels or lymphatics; in some instances I have also seen them in cells of a smaller type which it was not easy to differentiate from ordinary hyaline leucocytes, except that the nucleus of such cells was almost always in close contact with one portion of the cytoplasmic periphery, a rare occurrence in ordinary hyalines. I have not found them in polynuclears, eosinophiles, or lymphocytes. The cytoplasm of the cells which harboured inclusions was faintly basophile, and appeared somewhat coarsely reticular, much more so, at all events, than the clear hyaline cytoplasm of the large mononuclear leucocytes. Granules, as a rule, were not seen, but, in some instances, very fine granules, taking a reddish tint with the Romanowsky stain, were noted, seldom evenly distributed, but more often collected in irregular clumps or patches.

The inclusions themselves exhibit a considerable variation in shape, size and staining reaction, and their appearance may be gathered from the plate which I shew illustrating my first note, and also from the

examples which I have placed under the microscope. They do not resemble in any respect the azur granules of mononuclear leucocytes. They are small bodies, almost invariably circular in outline, and ranging from 1 to 5 microns in diameter, the great majority, however, measuring from 2 to 3 microns. They present themselves usually in one of two forms—a structureless, homogeneous form and a ring form; the former, which is the commoner, usually assumes a faint chromatin colour or a greyish tinge with the Romanowsky stain, and, more rarely, a deep chromatin tint. The ring forms, which are rarer, are almost always coloured a deep pink, similar to the chromatin of protozoa. In all cases the inclusions were embedded in the cytoplasm of the cell and not adhering to its periphery. At times the inclusions were seen to be lying in vacuoles, but more often this was not the case. The exceptionally large inclusions figured in connection with my first case I have not subsequently encountered.

As regards their frequency in a given case they are never abundant, several hours' search over a film frequently revealing only two or three. In the cases in which they were most numerous they were found in about one endothelial (?) cell in twenty. Cells containing several inclusions were more frequently seen than those with a solitary one.

Of the twelve cases of blackwater fever of which I have received blood films, I have found these inclusions in eight. In four cases I have failed to find them, although in two of these cases the cells of endothelial type were present in abundance. In one of the cases no endothelial cells were found, and the clinical details, which were scanty, suggested a considerable doubt as to the correctness of the diagnosis. Only in two cases could the inclusions be said to be fairly common.

Curiously enough, the most numerous inclusions which I found in the blood were in films from a case occurring in Uganda which were sent to me, not as blackwater fever, but under the suspicion that it had been one of kala azar. I found, however, no parasites of this nature, either in the blood or in smears made from the spleen and liver after death. The case was moribund on admission and died shortly after this, and, from the brief account of the symptoms and of what was found at the autopsy, there appeared nothing inconsistent with my suspicion that this, too, was a case of blackwater fever. If this were the case—a point impossible to

settle now—it would have been of interest from the presence of the inclusions calling attention to its true nature.

In considering the nature of these inclusions I am convinced from my study of them upon two points, that they are not artefacts and they have no connection with malarial parasites. Again, I have seen none which suggested to me the possibility of their being portions of nuclear material; nuclear extrusions or buds are by no means uncommon in connection with polynuclear and, less frequently, with mononuclear nuclei, but these are usually in close connection with the nucleus, and generally united to it by a thread of chromatin.

The possibility of these being fragments of altered erythrocytes, previously phagocyted by the cells which shew the inclusions, is one on which I am not able to speak with such confidence. The cells in question undoubtedly exhibit the power of erythro-phagocytosis, of which I have observed examples in three of these twelve cases. I have even, in two or three instances, noted both inclusions and a red corpuscle in the same cell. In spite of this I do not think that this is their explanation, since I have often observed the changes which phagocyted red cells undergo for instance, in the extensive phagocytosis of alien red cells, which can be readily studied *in vitro* by the opsonic technique, and I have never seen the remains of the red cell assume either the shape or the staining reaction of the majority of these inclusions. It is quite possible that the inclusions in question are not all of the same nature, indeed this is rendered almost a probability by the very considerable differences in shape, size and staining reaction which they exhibit.

Whether similar inclusions are to be encountered in the blood of other diseases, as has been suggested by Low,[9] is a point for the future to determine; I can only say at present, with a fairly large experience, that they are new to me.

I must next allude to another peculiar cell which I have encountered in seven out of these twelve cases of blackwater fever, and which, personally, I had never seen before. These cells I described in my second note as "chrome cells," from the extraordinary deep tint of chromatin colour which they assumed on Romanowsky staining; not only was the nucleus exceptionally darkly coloured, but the whole of the cytoplasm took on a lighter tint of the same red colour. Their nuclei were sometimes of polynuclear, sometimes of mononuclear type, and in size they

corresponded to the ordinary polynuclear leucocyte. In most instances the chromatin tint of the cytoplasm was deepest round the periphery of the cell, and I not infrequently noted an apparent diffusion of the red tint into the film surrounding the cell, although this was exhibited by no other type of cell in the particular film. In some cases the partial rupture of the cell allowed it to be seen that the cytoplasm had been filled with deep-staining chromatin granules, often in ring-form, and much larger than any of the usual types of granules encountered in leucocytes or marrow cells. I was at first inclined to regard these cells as being in some manner connected with the inclusions, but, since the publication of that note, I have received a communication from Dr. D. THOMSON, of the Liverpool Tropical School, in which he tells me he has observed similar cells in several different conditions, such as in Hodgkin's disease, in myelogenous leukæmia, sarcoma of the ileum, blood from leprosy nodules, and one or two others. Dr. THOMSON was good enough to send me some of his films, and to allow me to mention his as yet unpublished experience in this paper, for which I should like here to acknowledge my great indebtedness. Like myself, he had been much struck by their appearance, as he had never encountered them before nor seen them figured or described, and he was inclined to suspect that the granules were parasitic, but he tells me he is now inclined to regard them as some form of altered mast cell. However that may be, I was at least able to convince myself that some of the cells in his films were apparently identical with those that I described as "chrome cells," and it is thus clear that they have no specific relationship to blackwater fever. Since, however, such authorities as Sir RONALD ROSS and Professor ADAMI had never seen them, I have placed a specimen under one of the microscopes for you to see.

Returning to the inclusions and their possible nature, it was not unnatural that one should suspect that, like other inclusions, these might be an indication of the invasion of the cells by parasites of the class to which PROWAZEK has given the name *Chlamydozoa*. This view, with all reserve, I suggested in my earlier notes, and it is on this hypothesis that I wish to occupy the remainder of my paper. I should like, however, to make it quite clear that I put this hypothesis forward more by way of a suggestion than from any confident feeling that it is likely to meet with greater success than has been the lot of its innumerable pre-

decessors. The mere finding of certain cell inclusions in a few blood films may seem a slight foundation on which to raise a somewhat ambitious structure. At the same time I think an occasional excursion of this sort may at times be permitted to the research worker, whose daily lot is toil and disappointment. If, as I imagine, I find among you some who, like myself, are not altogether satisfied with the current explanations of the etiology of blackwater fever, I may perhaps claim from them a certain amount of sympathy, if not of agreement.

The chlamydozoa, of which our knowledge is still in its infancy, are a class of minute, ultra-microscopic organisms, capable of passing through the pores of very finely grained filter candles, and frequently associated with the presence of what are rather vaguely termed cell-inclusions. The best known diseases supposed to be caused by these organisms are variola and vaccinia, trachoma, molluscum contagiosum and bird-epithelioma. In addition to the above, however, it seems far from unlikely that rabies, scarlet fever, measles, chicken-pox, and perhaps yellow fever, may eventually be shewn to be due to organisms of this class. The cell-inclusions associated with molluscum contagiosum are the oldest known—the so-called molluscum bodies—but the Guarnieri's bodies of small pox and the Negri bodies of rabies are more widely known. At first taken for the actual particulate causes of the diseases with which they are associated, it soon came to be recognised that this position was not tenable, for one thing their comparatively large size was inconsistent with the proven filter-passing capacity of the viruses of these diseases, but at the same time they have, in some instances at least, come to be recognised as in a sense specific to the disease with which they are associated. As a matter of fact both the Negri bodies and Guarnieri's bodies are now held to be of considerable diagnostic value.

More recently certain extremely minute granules have been detected in the affected cells in trachoma, variola and molluscum contagiosum, and also in contagious epithelioma of birds, in rabies, in varicella and in both human and experimental scarlatina. Many of these observations are as yet lacking in detail and the very needful confirmation, but there appears little doubt that in some, if not all these diseases there occur, associated with the presence of the virus, extraordinarily minute granules, approaching the limits of microscopic visibility, and only demonstrable by special staining methods or by dark-ground illumination.

In some of the diseases in question the proof that these minute granules are in reality the particulate cause of the disease appears to me to be very strong, but naturally I have no time to enter into so large a subject. As to the association between these granules and the cell-inclusions, demonstrated in the various diseases, the views of PROWAZEK and others may be outlined as follows :—

A small granule enters a cell, for example a conjunctival cell in trachoma, a nerve cell in rabies, or an epidermal cell in small-pox, and causes a reaction in that particular cell which is evidenced by the surrounding of the invading granule by a mantle or cloak (hence the name, which is derived from χλαμὺς, a cloak) of some secretion which eventually becomes sufficiently abundant to be stained and recognised as a Guarnieri's body, a Negri body, a molluscum body, and so forth. To the buried granule, which may or may not be visible, is given the name "initial body." The initial body then commences to divide, and there are formed from it great numbers of extremely minute granules, which may eventually escape from the inclusion and fill the cytoplasm of the cell. These products of division of the initial body are called the "elementary bodies," and it is held that it is in this form that cell to cell infection is brought about, and that the virus is carried from host to host. To their minuteness are also attributed the filter-passing properties which, in a number of these diseases, have been clearly shown to be a feature of the virus.

In no instance can we yet say that we know all about the etiology of the diseases we have mentioned, but it appears to me that the evidence is accumulating which goes to shew that the chlamydozoa will eventually prove to be the cause of a number of diseases distinguished both for their variety and their severity.

I suggest then, that some, if not all, of these cell-inclusions which I have described, may be of the nature of the inclusions surrounding the "initial bodies" of chlamydozoa.

Let us now see what may be said in support of this hypothesis, and in how far it may be considered as not inconsistent with the established facts relating to blackwater fever.

At the outset we find that the principal objection to the idea of a specific virus, namely, that no such virus has been seen, no longer

applies, since the chlamydozoal hypothesis assumes the existence of an ultra-microscopical virus. Incidentally, it may be remarked that the hypothesis is not necessarily invalidated should it be proved that the inclusions to which I have drawn your attention are capable of some other interpretation.

The clinical dissimilarity between blackwater fever and the diseases associated with chlamydozoa is freely admitted, but, on the other hand, the lack of resemblance is scarcely greater than we find among those diseases themselves.

The majority of the chlamydozoal affections are extremely infectious and tend to spread in epidemic form. I have suggested elsewhere that this apparent discrepancy may be explicable if we assume that the ultra-microscopical virus of blackwater fever is limited to tissues and cells in the deeper parts of the body, in contrast to the known superficial site of the virus—for instance, in the skin lesions and affected mucous membranes of variola, molluscum contagiosum and trachoma.

Further comparisons of this sort, however, would not, I think, help us much, since definite knowledge of the nature and mode of action of the chlamydozoa is still lacking, and, until this is available, it will be obvious that attempts to compare the known factors in connection with blackwater fever with the uncertain factors of these little-known micro-organisms would lack point and precision. I propose then to limit this comparison to an examination of the conclusions reached in the first portion of my paper in the light of the chlamydozoal hypothesis. We shall deal with them in the order in which I placed them there.

1. The general agreement that blackwater fever is only encountered in those who have either suffered from malaria or who have lived for some time in a country in which they must constantly have been exposed to malarial infection. This appears to me to be the best established fact in connection with the disease, and unless a reasonable explanation is forthcoming, co-ordinating this fact with any new hypothesis, the latter must be regarded as untenable.

I would suggest that this association with malaria is comprehensible if we assume that the chlamydozoal virus is one which is transmitted either by the same insect which transmits the malarial parasite, or by a different insect whose habits and bionomics correspond closely to those of mosquitoes and whose geographical distribution is similar. I do not

claim any novelty for this suggestion, which must have occurred to many, but I think its possibility is enhanced in the light of the chlamydozoal hypothesis. We know already that mosquitoes transmit at least four diseases, malaria, yellow fever, filariasis and dengue, so it is not asking much to assume them capable of transmitting a fifth. If we assume further that the virus of blackwater fever is a rare parasite of mosquitoes in comparison with malaria, or that it is possibly limited more strictly than the latter to one or two species of mosquitoes, it is not difficult to account for many of the puzzling anomalies in connection with the malarial hypothesis—for instance, the facts that there is no direct relationship between the number of the malarial parasites in the blood and the severity of the paroxysm of hæmoglobinuric fever, and that quinine has no effect in aborting or curing the attack.

I am also inclined to regard as significant the fact that two out of the four mosquito-transmitted diseases are shown to be due to filter-passing viruses, namely, yellow fever and dengue, while the virus of phlebotomus or three-day fever, transmitted by phlebotomus papatassii, is another instance of the same nature.

2. The second conclusion, referring to the immunity of natives in endemic areas, and the greater susceptibility of whites and of alien natives introduced into endemic areas, is not inconsistent with the new hypothesis on the assumption that immunity follows the same lines in the two diseases. If the virus of blackwater fever is much more rare than that of malaria, as we have suggested above, we have here an easy explanation of the fact that, as a rule, new comers are not attacked, and that prolonged residence is a feature in the incidence of the disease.

3. The conclusion that immunity to malaria appears to go hand in hand with blackwater fever and that the measures which protect against the one are also effective against the other, supports the idea that the virus of the latter is also transmitted by a biting insect, similar in its habits to the mosquito.

4. The fourth conclusion that there are apparent discrepancies in the geographical distribution of the two diseases, but that blackwater fever only occurs in intensely malarious countries is also explicable on the above assumption of a specific virus transmitted by some insect with a life habit resembling the mosquito, but either less numerous or more restricted in its geographical distribution. The rarity or absence of

blackwater fever in certain districts heavily infected with malaria would thus find an explanation either in the absence of the particular transmitting species or in the fact that the carrier in that district was not at the time infected with the virus.

5. The conclusion that some exciting or secondary cause is needed would appear to await further understanding and explanation, as is also the case with the sixth conclusion, relating to the mechanism of the production of hæmolysis. These two are evidently closely connected, and it is probable that a common explanation underlies both. It is I think clear that, even if the chlamydozoal hypothesis were correct, we should still find that secondary or exciting causes played a part in the production of the sudden and extensive hæmolysis. For example, there are cases on record in which a first attack of blackwater fever has occurred some weeks after the individual has left the endemic area and returned to a temperate country. Such cases would suggest, on this hypothesis, either that the virus had an exceptionally long period of latency, which appears improbable, or that infection with the virus was not *necessarily* accompanied by the symptom of hæmoglobinuria.

I think it appears from the above consideration of the agreed facts relating to blackwater fever, in the light of the chlamydozoal hypothesis, that there are none which are definitely antagonistic to its possible correctness while there are some which would render our comprehension of these facts distinctly more easy. I have no wish, as I have said, to build too heavy a superstructure upon a foundation which I admit is very far from stable, and I have put it before you principally as a suggestion and that I may have the benefit of your criticism.

At the risk of your deeming me too fanciful I venture, in conclusion to suggest that there is yet another way in which the connection between malaria and blackwater fever might conceivably be brought about. I can see no reason why we should deny the possibility of the malarial parasite itself being subject to disease. The further we progress in microscopical research the more inconceivably minute structures come to our knowledge, either by direct observation or by inference, and to my mind it is a bolder thing to assert that we have reached the limits of particulate life than to admit the possibility that there yet remain forms of life smaller even than the chlamydozon granule.

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DISCUSSION.

Dr. C. F. HARFORD: In the absence of any distinct test for blackwater fever, the symptomatology and the general facts concerning the disease are very important, and on this account I desire to offer a few remarks, especially as I have had three attacks of this fever myself. The first thing I would say is that the question of diagnosis is of the utmost importance. I cannot help thinking that hæmoglobinuria is a subject very little understood, and that people have been far too ready to speak of all cases of hæmoglobinuria as if they were blackwater fever, and also I cannot help feeling that hæmoglobinuria is due to many different causes, and that it may occur in many other diseases. Undoubtedly there are other special symptoms besides hæmoglobinuria, which go to form the disease we are now speaking of as blackwater fever. At the same time hæmoglobinuria is the prominent symptom. Now I believe it is an undoubted fact that this disease has spread fairly rapidly within the last 20 to 25 years, during which it has been definitely studied. I suppose we may say it is generally recognised that the disease was first

identified in West Africa, and I think the first work on the subject was that very remarkable French monograph by Monsieur BERANGER FERAUD. Well, since then it seems that the disease has spread to other parts, and especially to East Africa and to other parts of the world. The idea that the disease has been present all over the world, such as it is to-day, but that it has not been identified, seems to me to be quite an impossible hypothesis. I say it has spread in various ways from one country to another just as parasitic diseases do, perhaps due to increased contact between different races. For my own part I am still absolutely of the opinion that it is practically malaria, or a certain form of malaria, in which there has been a special complication of hæmoglobinuria occurring. It seems to me that we are too ready to regard malaria as a disease about which we know everything. I venture to say that it is not so. We are waiting every day for greater information about malaria, and there are perhaps even greater varieties than we suppose. When we think of this fact that natives coming from one part of the world where malaria is rife and going to another part, although they appeared to be immune in their native country, yet in their new environment they contract malaria almost in the same way as Europeans or white races, this rather suggests to me a difference between malaria in different parts of the world, and that it is quite possible that blackwater fever may be associated with a special form of malaria we have not yet fully understood. There is another fact that I think is important. There are many people who have had malaria abroad, and never blackwater fever, and they come to England and then contract blackwater fever for the first time. I consider that this is the result of a complication brought on in people infected with malignant malaria who have been careless about the taking of quinine. As to the question of how soon people get blackwater fever after entering a malarious region, I certainly think it is a most remarkable fact that in the majority of cases they do not get it until they have been a considerable time in the country. As regards the question of quinine having no effect, I venture to dispute that. I always took quinine in my attacks with the greatest possible success, and it always effected very great good. The late Dr. CROSSE, who in this room introduced this subject many years ago, and had a large experience, always gave quinine, and with the best results. I do not encourage people to give quinine, because it is regarded as the wrong

thing to do, and one does not advise people to go against the generally accepted view. I believe that this is largely due to a prejudice against quinine, because of the idea that quinine produces the disease, and because parasites are not present during an attack. I do not think it is at all proved that quinine has no effect in aborting an attack, although in some cases it may increase the hæmoglobinuria symptoms.

As regards other diseases, which may be associated with the disease, I should include African tick fever. Dr. A. R. and Dr. J. H. Cook, in Uganda, have shewn various cases in which it appears that blackwater fever has been associated with tick fever. I know of two cases, old students of mine, who suffered from tick fever in Africa and came home to England, and both of them died from blackwater fever very shortly after their return to Africa.

Dr. F. M. Sandwith: Sir, you say that you trust your remarks may call forth expressions of dissent or agreement. While I am in agreement generally with this most valuable paper, may I mention a few points with which my experience is not in accord.

Under the heading (1.) there is a paragraph which I perhaps do not quite understand. It looks to me almost as if the question had been begged, which I am sure you do not desire. I believe that malaria is the chief essential for producing blackwater fever, plus something else as well.

Then a little lower down,—"an attack is altogether uninfluenced by quinine." I confess I do not understand that paragraph, or, if I do, I do not agree with it. On the contrary I think an attack is sometimes dangerously influenced by quinine. If it means, as I think it does, that hæmoglobinuric fever cannot suddenly be put an end to by two or three large doses of quinine, that is what we should all believe. If, however, the argument is that hæmoglobinuric fever cannot suddenly have the temperature reduced by quinine in the same way that the temperature in malaria can be by quinine, as some of us believe that hæmoglobinuric fever is a complication of malaria, may we not compare it with other diseases where the complications are not affected by the treatment which cures the original disease? Perhaps it is too unfair to take syphilis. We know we can cure syphilis in this country if we give sufficiently large and early and prolonged doses of mercury or salvarsan, or,

I should say, salvarsan plus mercury. But if you take general paralysis or locomotor ataxy we are not able to meet with equal success. I know these are much more chronic diseases than blackwater fever. The suggestion that hæmoglobinuric fever is a complication of malaria must not be put aside because it is not to be cured in the same way as malaria. We all know, moreover, that malaria cannot be cured by any short treatment. Possibly the futility of the special anti-toxin in diphtherial peripheral neuritis is a better analogy.

Then I suppose in this discussion we put aside altogether those most interesting cases where people have a special idiosyncrasy against quinine. They are not met with very commonly. I had an interesting case once. A woman came to me once and asked for a tonic, and I gave her 2 grain doses of quinine three times a day. She sent for me after two days and I found her lying in bed, bleeding from the mouth, with many large petechiæ on face and limbs, and to gain time I said, "Have you had this before?" She said, "Once, after a tonic." I looked up the prescription for that tonic and found it also was quinine. These cases are very important to us who have to select recruits for the tropics in this country. I do not say they ought to be included in the group we are now considering.

Then you say that "No cases have been recorded in non-malarious countries in which quinine, given for some other disease, has caused blackwater fever." I do not say I can produce a case of that, but a man came to see me once who was an Administrator in East Africa or Central Africa,—he is still out there. He said he was perfectly well himself, but he had been sent to me by a medical relation of his to ask a question. It appeared he had in Africa a large out-patient practice, he bound up wounds, set broken limbs, administered drugs, for there was no doctor in his area; but there was one disease he did not know how to treat and that was blackwater fever. I told him what little we knew about it, and he then began talking about malaria, and he said, "Of course I have had malaria, but I have never had blackwater fever." I said, "What grounds have you for supposing you have not malaria now?" I examined him and found parasites in his blood, and then, in my ignorance (for it was some years ago) I did a wrong thing, which I publicly desire to confess. I gave him 10 grains of quinine three times a day, the maximum dose, 30 grains, because he wanted to leave this country in three

days. He went home and developed blackwater fever. I am perfectly certain my quinine gave him that inconvenient attack. Eventually I gave him ½ grain of quinine and increased the dose to 2 to 3 grains, and eventually got him up to 10 grains three times a day. He was cured of the malaria in time and has certainly not had blackwater fever since. He expressed eternal gratitude and I used to hear from him, but that eternal gratitude only lasted for two years. The quinine certainly produced the blackwater fever. There may be others present in the room who have had that experience and would like to make similar confession, but we may forgive them if they do not do so.

"There appears to be no relation between the size of the dose, the channel of administration, or the particular salt employed." On the contrary I find the size of the dose is very important. If you want to produce blackwater fever, you have got to choose your case carefully, and you must select a person who has had lots of attacks of neglected subtertian malaria, and has not taken quinine lately. Then give him a a large dose of quinine and watch the result. If unsuccessful, you must add next time a long railway journey or exposure to rain.

Then with regard to cases of new-comers being attacked. Well, surely these cases, if they are absolutely reliable, are the exceptions which prove the rule. In a Missionary Society in Central Africa, with which I am connected, it was found that so many recruits going to Africa got blackwater fever in the *third* year that the rule was made that they should not go out for the first period for a longer term than two years. Since that rule was made, ten years ago, there has only been one case of blackwater fever in a recruit, which unfortunately proved fatal. He had only been in the country for ten months—the earliest case I know. He was an extremely young man, under 22 years old. During the ten months he had had several short attacks of malaria; the fatal one was treated with 20 grains of quinine on the first day before the urine was black.

Now as to the geographical distribution. Nobody knows better than yourself, Sir, that we do not pretend that all parts of the world where malaria exists can produce blackwater fever. The suggestion is that in those parts of the world where malaria is rife, and where the more pernicious type of malaria exists, and where prophylactic quinine is not taken daily, there you are more likely to find blackwater fever. Every

Anglo-African on the West Coast knows all about malaria, nearly every Anglo-Indian snaps his fingers at it, and the Government to-day does not provide mosquito nets in barracks for the white troops. In the case of Africa, the malaria kills, and a man may see there from his compound evidences of the deaths of his predecessors. The Anglo-Indian does not see his white friends dying of malaria, and he has not as yet a great dread of it.

I venture to think that the views of DEEKS and JAMES, quoted under paragraphs 1 to 5, are what we can agree with. I except perhaps No. 3, which says, "it may be determined by any depressing influence."

On page 10, No. 2.—"Negro and other native races inhabiting endemic zones exhibit a certain degree of immunity." I dare say they do, it is impossible to say, but I do ask those present from Central and East Africa whether blackwater fever is not a fairly common disease among the natives. The Administrator whom I have mentioned, had only negroes as patients, and he told me that the servants got it, his labourers got it, and the people came to him because the negroes suffered from blackwater fever. I venture to think that the blacks seemed not to get malaria because we looked for it at the wrong age. There is one thing that is puzzling to me. A white missionary, with a white wife, living in Africa, under the same roof, eating the same food under the same conditions, both get malaria, but are equally careless about quinine, and yet only one gets blackwater fever. This I suppose is due to some idiosyncrasy which is present in the one and not in the other. Sex, I believe, has nothing to do with the matter.

May I say something about the interesting cases which you sometimes see of blackwater fever without hæmoglobinuria? I mean by that the usual clinical symptoms of vomiting, fever, rigors, jaundice, enlarged spleen, and all the symptoms except blackwater. I had a very instructive case some time ago of a man who telegraphed to the Tropical School, and said, "Will you send someone down, an expert, to see a case of bilious vomiting, high coloured urine, fever and rigors?" which had occurred in an individual just returned from Nigeria. I jumped to the conclusion it was a case of blackwater fever. I was the only person on the spot, and I went and saw this case. The man had no hæmoglobinuria. The general practitioner told me the patient was an engineer, who had lately buried his brother and a friend from blackwater fever in

Nigeria, and that he had it. I said to the general practitioner, "It seems to me he has all the symptoms except hæmoglobinuria." I advised him not to give quinine so long as the acute symptoms were present. A month later, when the patient was safely taking quinine, he had an attack of blackwater fever, and I have no doubt that the condition which I saw was a preliminary stage of it, and it was only my instinct that postponed the attack. I have seen two other cases in England where hæmoglobin was absent (and remained absent), but blackwater fever seemed to be impending.

Dr. A. J. CHALMERS: As a medical man on the West Coast of Africa many years ago, and afterwards in Ceylon, I should like to make a few remarks. First of all, with regard to the West Coast of Africa, I found I could recognise blackwater fever there, but when I got to Ceylon, where I was for ten years, I failed to recognise the disease. If blackwater fever was caused by malaria why did I not find a case in Ceylon, where malaria is common? I admit that recently they have said a case occurred there, but I fancy that was a case of malarial hæmoglobinuria. My views, which I have expressed on several occasions, are, that blackwater fever is a disease *sui generis*, and that there may be a quinine hæmoglobinuria and a malarial hæmoglobinuria. Take my own case: I was badly infected with malaria in the fighting round Coomassie, and I had a severe attack of malaria. In Ceylon I have taken at different times quinine in various doses, and for a long time I was free from malaria. In a stress of work I found I was getting feebler, and I examined my blood and found it full of the small rings of the tropical parasite. I took some quinine on and off for about a week or two, and then I developed a really severe attack of malaria, with a fairly high temperature, which would not come down. You are all very well aware of the dictum that fever which does not come down after a quinine treatment in four days is not malaria, but my temperature did not go down until I had a large dose of quinine, that is, a gramme by the mouth and two grammes by intra-muscular injection. Now that was a fairly large dose, the injection and the dose by the mouth make in all three grammes; but it certainly cured me, and I did not get any blackwater fever. This is a case where neither repeated small doses of quinine nor the large dose have produced blackwater fever, and yet I have lived in a

blackwater fever district on the Gold Coast, where I worked for four years. Coming to another point: I have examined the specimens which have been put out under the microscope and I have been very deeply interested in them. I have somewhat a suspicion concerning one of the bodies; it seems to me to rather resemble Plimmer's bodies. I refer to the specimen under the first microscope, in which bodies are seen resembling those which many years ago Mr. PLIMMER described in cancer, and with which I was acquainted at that time. Personally I cannot believe that malaria *per se* is the cause of blackwater fever. I have attended cases where I knew perfectly well if I gave even a grain of quinine that the person would develop hæmoglobinuria; but if I administered calcium chloride and then quinine there would be no hæmoglobinuria. Surely that is not blackwater fever? I cannot believe that a medical man who has lived on the West Coast, and who has seen true blackwater fever, would make a mistake between blackwater fever and this hæmoglobinuria, which is a totally different thing, and to talk about a person having two or three attacks of blackwater fever in one year and living is to my mind impossible. They can have two or three attacks of hæmoglobinuria and live, but from the severe cases I saw, I could hardly credit they could live after a number of attacks of blackwater fever. I have always looked upon the disease as being possibly a protozoal infection, and I certainly regarded mosquitoes on the West Coast with suspicion, and I dissected a number with negative results.

I wish to thank Sir WILLIAM LEISHMAN very much for his excellent demonstration this evening.

Dr. C. M. WENYON: I am sure we are very much indebted to our President for the lucid way in which he has explained his theory of blackwater fever. We have been reminded that Dr. SAMBON first suggested that this disease might be due to some parasite which would probably prove to be a piroplasma, since the disease caused by these parasites resembled blackwater fever in many ways. Unfortunately no one has been able to find such a parasite. Sir WILLIAM LEISHMAN now offers another suggestion. Though it is not a piroplasma which is responsible for blackwater fever, it is some other parasite, possibly some invisible organism to be classed with the chlamydozoa.

It is interesting to note how the chlamydozoa theory occurred to

Sir WILLIAM LEISHMAN. Certain chromatin staining granules were found in large mononuclear cells, probably of endothelial origin, in some blood films from a case of blackwater fever. These granules resembled other granules which are developed in certain diseases as a result of a chlamydozoa infection. On the strength of this resemblance, Sir WILLIAM LEISHMAN builds up the fascinating theory which has been explained to us this evening. Yet though it was these granules—specimens of which are to be seen under the microscopes at the top of the room—which suggested the theory, it is a little disappointing to hear that Sir WILLIAM LEISHMAN is far from asserting that they are the primary cause of blackwater fever. This being the case, it appears that there is very little, if any, evidence in support of the chlamydozoa theory, or that the granules in question are in any way connected with these parasites.

With regard to the structure of the granules I have very little to say. It must be evident to those who have had much experience in blood examinations that granules of this kind may be passed over quite readily. Now that attention has been drawn to them, they will probably be found to be of fairly frequent occurrence. A peculiar arrangement of the nuclei in a human trypanosome suggested that it was a new species, and this peculiarity was supposed to be diagnostic. Attention having been drawn to these forms, similar examples were found to occur in the case of other well-known trypanosomes which have been for years under the observations of the expert, who has either missed or neglected to record the forms shewing these features.

Under one microscope are examples of two large bodies within a cell. I cannot say definitely what they are, but I am quite familiar with them, as I have seen exactly similar structures in smears I have examined. We have been told that the endothelial cells may ingest red-blood corpuscles, and that normoblasts may occur in the blood of blackwater fever cases. May not the granules be derived from the nuclei of ingested normoblasts?

Major S. LYLE CUMMINS: There is one point that rather supports your theory, Sir, that has not been touched upon by any of the other speakers, and I think it should be mentioned. The point is there does seem to be occasionally a *series* of cases of blackwater fever which follow each other giving the impression that there may be some connection between one

case and the next. For instance, an Egyptian orderly was sent to nurse a Roman Catholic Missionary. The orderly was down with blackwater fever in the course of a few weeks. In another case, an Egyptian orderly was sent down the Nile with a sick officer. The officer developed blackwater fever on the way, and the orderly very shortly afterwards developed blackwater fever also. These are not absolutely isolated instances.

In 1902, the first case of blackwater fever that came under my notice at Wau, occurred on the 4th July. In a week I had a second, and in three more days a third case. Then it stopped, and no more cases occurred at that station during the year, although ordinary malarial attacks were common.

These points certainly add something in favour of the theory that there may be some causative agent at work other than malaria. But nevertheless I feel obliged to add that neither these points nor the evidence adduced to-night in favour of some protozoal cause other than malaria, seem to me sufficient to justify the view that blackwater fever is not connected with malaria. The "bodies" shewn under the microscopes at this meeting, if parasitic, are parasites of certain kinds of leucocytes, whereas the lesion in blackwater fever is a destruction of red corpuscles—a condition more likely to be brought about by a parasite of the red cells, such as the malarial parasite. The idea has occurred to me that a dose of quinine, given at a certain moment of a severe malarial infection, may so far alter the young parasites that they come to a premature end shortly after gaining their hosts, the red corpuscles. The infected corpuscles, in their turn, may be destroyed by the breaking down of the contained malarial parasites under the influence of quinine. I believe that blackwater fever can only occur under the influence of quinine, and in persons severely infected with malaria.

Fleet-Surgeon P. W. Bassett-Smith: Something has been said about latency and the difficulty of diagnosis in blackwater fever. It may be of interest to quote a case that occurred in the navy some time ago. A man, aged 30, healthy, a petty officer. He had been employed on the West Coast of Africa for two years, and had been 13 weeks in the Benin river and had fairly good health. He came home in 1900, and in September, 1905, he had an acute attack of hæmoglobinuric fever, the temperature running up high. Next year, about the same time, he had

a second attack, and in November of the same year, he had a third attack of hæmoglobinuria, temperature 104·8, marked rigors, and certain amount of gastric discomfort, with irregular fever, lasting ten days. This man was examined for malaria parasites and none were found. He was given quinine, and it neither diminished nor increased the symptoms; at any rate it did not bring on hæmoglobinuria when given after the symptoms had ceased. Whether the case might possibly be one of blackwater fever having a long latent period in a man who had been subject to malaria, or whether it was an ordinary paroxysmal hæmoglobinuria occurring in England is a difficult thing to say. The onset of the attack in each instance was brought on by cold, the last time it was a snowy morning, and the initial cause of the onset was undoubtedly a severe chill.

The PRESIDENT: In view of the lateness of the hour, I do not propose to make a lengthy response. One of my objects in bringing forward the subject of blackwater fever was to elicit opinions from the Fellows with a view to finding how far they were in agreement as to its etiology. The result has shewn very clearly that there is little or no agreement upon this important point, and there have been few points of view advocated this evening by individual Fellows which have not been strongly controverted by the experiences related by other speakers. I explained in my paper that, apart from the chlamydozoal hypothesis, the tentative conclusions which I had put forward were not the results of my own very limited personal acquaintance with the disease, but were framed upon a study of a very large portion of the recent literature on the subject; on this account I was unable to attach more than a fractional value to individual views, such, for instance, as that of Dr. SANDWITH. I share Dr. SAMBON'S difficulty in tracing any obvious connection between the various forms of cell-inclusion, which I have demonstrated under the microscopes, and am personally inclined to regard the large inclusions, which I have only encountered once, as being different in nature from the common type of small inclusions. Dr. CHALMERS suggested that these large forms resembled Plimmer's bodies; I think this is hardly likely, since I have studied the latter closely some years ago, and there were several important points of morphological distinction between them. Dr. WENYON'S suggestion that the smaller inclusions might

represent the nuclear remains of ingested normoblasts had already been made to me verbally by Sir RONALD ROSS, but for several reasons I do not think it likely that this could be their origin. I am grateful to the Fellows for so freely expressing their views, and especially those whose criticisms have been directed to the cell-inclusions.

Dr. SAMBON also took part in the discussion.

NOTICES OF MEETINGS.

The next Ordinary Meeting of the Society will be held at 11, Chandos Street, Cavendish Square, W., at 8.30 p.m., on Friday, December 20th, 1912, when a paper will be read by Dr. A. CASTELLANI, on "Vaccination with live vaccines for Typhoid, Dysentery and Cholera," who will also give a demonstration of various fungi producing disease in the tropics.

At the Meeting of the Society on January 17th, 1913, a paper will be read by Dr. A. G. BAGSHAWE, on "Recent Advances in our Knowledge of Sleeping Sickness."

EDITORIAL NOTICES.

The Editor of the TRANSACTIONS will be pleased to receive short papers to be included under the heading of "Notes and Comments," or "Questions," in addition to longer papers on subjects of Tropical interest, which may be offered for presentation at meetings of the Society. He will also be glad to receive books for review.

Any communications for the Editor should be addressed to THE EDITOR of the TRANSACTIONS of the Society of Tropical Medicine and Hygiene, 11, Chandos Street, Cavendish Square, W.

ELECTION OF FELLOWS.

The following were duly elected Fellows of the Society :—

A. R. CONTRACTOR, M.D., London.

J. E. L. JOHNSTON, M.B., Ealing.

E. M. PARSONS-SMITH, M.B., Khartoum.

Captain D. S. SKELTON, M.R.C.S., R.A.M.C., Zanzibar.

EXCHANGES.

Annali di Medicina Navale e Coloniale.

Archives de l'Institut Pasteur Tunis.

Archives fur Schiffs und Tropenhygiene.

Archivos do Real Instituto Bacteriologico Camara Pestana.

Bulletin Public Health and Marine Hospital Service of the U.S.

Bulletin of the Sleeping Sickness Bureau.

Bulletin de la Société de Pathologie Exotique.

Bulletin de la Société Portuguaise des Sciences Naturelles.

Bulletin de l'Academie Royale de Médecine de Belgique.

het Geneeskundig tydschrift voor Nederlandsch-Indie.

Indian Civil Veterinary Department Memoirs.

Johns Hopkins Hospital Bulletin.

Journal of Meat and Milk Hygiene.

Journal of Tropical Veterinary Science.

L'Enseignement Medico Mutuel Internationale.

Memorias do Instituto Oswaldo Cruz.

Philippine Journal of Science.

Revue de Médecine et d'Hygiene Tropicales.

Sanidad y Beneficencia.

Veterinary News.

NOTE.—The above publications lie on the Library table at 11, Chandos Street, and are at the disposal of Fellows.

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